



**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Docket No: Q88273

Pyare L. SETH

Appln. No.: 10/540,422

Group Art Unit: 1614

Confirmation No.: 4203

Examiner: Lezah ROBERTS

Filed: April 4, 2006

For: PHARMACEUTICAL LIQUID COMPOSITION CONTAINING PYRIDONE  
DERIVATIVE

**DECLARATION UNDER 37 C.F.R. § 1.132**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Dr. Pyare Seth, hereby declare and state:

THAT I am a citizen of India;

THAT I have received a research degree of Doctor of Sciences in 1955 from the Swiss  
Federal Institute of Technology School of Pharmacy; and

THAT I am the inventor of the above-identified application and I am familiar with the  
subject matter thereof.

I am also familiar with the Action dated June 11, 2007 and the Advisory Action dated  
October 3, 2007.

Further to the Response filed November 2, 2007, I submit the following in support of the  
patentability of the present application.

The Examiner takes the position that Margolin teaches an ointment, which can be a liquid, inhalable fluids, eye drops (which are liquids) and therefore it is reasonable to conclude that the composition comprises a solvent which is able to dissolve the pyridones as claimed.

It is respectfully submitted that Margolin is not enabling for how to make and/or use a "liquid composition" comprising pirlfenidone, much less a liquid composition comprising pirlfenidone at a concentration of 10-25% as in the present invention.

Margolin merely lists a number of theoretical dosage forms, which are applicable to most active ingredients, without any indication as to how to prepare such dosage forms and which inactive ingredients or excipients to use. Also, Margolin does not exemplify any specific "liquid preparations" or suitable solvents for any such preparations.

The test examples 1 and 2 given in the Margolin patent are said to refer to a Capsule dosage form (Example 1) and a Hydrophilic Ointment (Example 2) which are apparently the basis of rejection of the present claims. Both the examples given do not contain either any composition or any method of their preparation which may be reproducible by any person of ordinary skill in the art. Apart from this deficiency of a complete lack of the important information, the close examination of the examples by a technical person acquainted in the skill of the art, these examples are completely misleading as will be seen from the following.

Example 1 of Margolin : Capsule Formulation

Example 1 of Margolin et al is a capsule formulation, which merely states that 800 mg, 1200 mg or 1600 mg of pirfenidone is contained. For purposes of therapeutic use a drug is very seldom (almost never) used as such (without excipients necessary for disintegration of the capsule in the stomach to release the drug out of the capsule) and in case of Example 1, the capsule does not contain any composition whatsoever. Thus, the capsule of the Example 1 would not be expected by those of ordinary skill in the art to show any therapeutic effect in the body and is possibly ineffective.

Example 2 of Margolin: Hydrophilic Ointment (Cream)

There is no description of how to prepare a Hydrophilic Ointment (Cream)<sup>1</sup> containing 5 to 10% pirfenidone as mentioned in Example 2 of Margolin et al, which is apparently the basis of rejection of the present claims. Example 2 merely states, "hydrophilic ointment containing 5 to 10% pirfenidone". There is no composition or method of preparation for such a "Hydrophilic Cream" given under this example. If one takes the example from Remington's Pharmaceutical Sciences book page 1304 (Chapter 68) where a composition and method of preparation for such "Hydrophilic Ointment" is given, it would not be possible for one of ordinary skill in the art to prepare a cream having a high concentration of pirfenidone as recited in the present claims. This is primarily because a drug must be soluble in water before it can be incorporated as given under

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<sup>1</sup> As noted in The United States Pharmacopeia reference (previously submitted as an attachment to the request for Reconsideration filed November 2, 2007) at page 1944, 2<sup>nd</sup> column lines 1-2 under the heading "Water-removable Bases", hydrophilic ointment is correctly called a "cream".

the method of preparation given in Remington's Pharmaceutical Sciences. Otherwise, if any other organic liquid is used in place of or together with water, it must not be an irritant (such as alcohol) and it must be otherwise permissible and of a pharmaceutical quality and also have a good solubility to permit incorporation of 5 – 10% of a drug like pirlfenidone (which is very poorly soluble in water). Moreover such a solvent should not dissolve the emulgator and other constituents of the emulsion. As such the description of Margolin is not a sufficient teaching or guidance for one of ordinary skill in the art to make a hydrophilic cream containing 5-10% of pirlfenidone, much less a liquid preparation containing 10-25% pirlfenidone as in the present claims.

As noted in the present specification, before my invention, the highest possible concentration of the active ingredient, pirlfenidone reportedly dissolved, is 7% without recrystallization. Also previous attempts to make more concentrated liquid formulations containing pirlfenidone using alcohol-based solvents have failed<sup>3</sup> and the solvents used irritate the mucous membrane resulting in open wounds and pain, which is unacceptable.

Keeping in view the difficulties pointed out above, the examples given in the Margolin patent are inoperative and not enabling for a liquid pharmaceutical composition comprising pirlfenidone and a solvent capable of dissolving pirlfenidone in a concentration of an amount of 10-25% by weight. None of the other references mentioned by the Examiner remedy this deficiency as none of these references even recognize the problem of obtaining a liquid composition having a high concentration of pirlfenidone within the presently claimed range.

On the other hand, the present invention is directed to a pharmaceutical liquid composition comprising pirlfenidone in a high concentration of 10-25% by weight in a

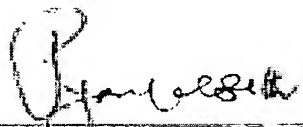
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pharmacopieal permissible liquid, which as a useful and novel innovation to provide a "universal dosage form" for this important "orphan drug" – Pirfenidone.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Dec. 11, 2007

  
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Dr. Pyare Seth